JACC Vol. 13, No. 6
May 1989:1377–81

REPORTS ON HYPERTENSION

Pathophysiologic Assessment of Left Ventricular Hypertrophy and Strain in Asymptomatic Patients With Essential Hypertension

STUART D. PRINGLE, MB, ChB, MRCP,* PETER W. MACFARLANE, BSc, PhD,*
JAMES H. McKILLOP, PhD, FRCP,* A. ROSS LORIMER, MD, FRCP,*
FRANCIS G. DUNN, FRCP, FACC†
Glasgow, Scotland

To investigate the significance of the electrocardiographic (ECG) pattern of left ventricular hypertrophy and strain, two groups of asymptomatic patients with essential hypertension were compared. The patients were similar in terms of age, smoking habit, serum cholesterol and blood pressure levels, but differed in the presence (Group I, n = 23) or absence (Group II, n = 23) of the ECG pattern of left ventricular hypertrophy and strain. Group I patients had significantly more episodes of exercise-induced ST segment depression (14 versus 4, $p < 0.05$) and reversible thallium perfusion abnormalities (11 of 23 versus 3 of 23, $p < 0.05$) despite similar exercise capacity and absence of chest pain.

Nonsustained ventricular tachycardia was detected on 24 h ambulatory ECG monitoring in two patients in Group I, but no patient in Group II. Coronary arteriography performed in 20 Group I patients demonstrated significant coronary artery disease in 8 patients.

This study has shown that there is a subgroup of hypertensive patients with ECG left ventricular hypertrophy and strain who have covert coronary artery disease. This can be detected by thallium perfusion scintigraphy, and may contribute to the increased risk known to be associated with this ECG abnormality.

(J Am Coll Cardiol 1989;13:1377–81)

Although the term left ventricular hypertrophy and strain has been in use for over 30 years, its underlying pathogenesis remains unclear. Undoubtedly, however, it represents a potent marker for subsequent cardiovascular events (1). The Framingham Study (2) and the British Regional Heart Study (3) have shown that a pattern of left ventricular hypertrophy and strain on the electrocardiogram confers a risk equivalent to that of a previous myocardial infarction. Furthermore, the risk is greater than that due to the blood pressure level itself (1). Could unexpected coronary artery disease explain this risk in these patients, or is it a consequence of myocardial ischemia due to more excessive degrees of left ventricular hypertrophy? The purpose of this study was to conduct, by detailed noninvasive and invasive means, an assessment of asymptomatic patients with left ventricular hypertrophy and strain in order to determine the relative contribution of coronary artery disease and left ventricular hypertrophy itself to the electrocardiographic (ECG) strain pattern.

Methods

Study patients. The study group comprised 46 patients with essential hypertension (38 men and 8 women), whose mean age was 48.2 years (ranged 32 to 65). All patients were asymptomatic at selection and, in particular, there was no clinical evidence of ischemic heart, cerebrovascular or renal disease. Asymptomatic patients were chosen to prevent bias in selecting patients with an increased likelihood of having coronary artery disease. Antihypertensive medication was withdrawn for 1 week before the noninvasive investigations, which were all performed within a 48 h period. The following investigations were made.

Blood pressure. Blood pressure was measured throughout the study with a standard cuff and sphygmomanometer. Basal blood pressure was defined as the mean of two readings taken at the beginning of each study day after the patient had rested quietly for 15 min.

From the *University Departments of Medical Cardiology and Medicine, Royal Infirmary and †Department of Medical Cardiology, Stobhill General Hospital, Glasgow, Scotland. This work was presented at the 36th Annual Scientific Session of the American College of Cardiology, New Orleans, Louisiana, March 8 to 12, 1987. It was supported by Grant 84-10 from the British Heart Foundation, London.

Manuscript received July 11, 1988; revised manuscript received November 11, 1988, accepted December 15, 1988.

Address for reprints: Stuart D. Pringle, MD, University Department of Medical Cardiology, Royal Infirmary, 10 Alexandra Parade, Glasgow G31 2ER, Scotland.

0735-1097/89/$3.50

JACC Vol. 13, No. 6
May 1989:1377–81

Electrocardiography. The 12 lead ECGs were recorded and voltages determined using the Glasgow CARE (Computer-Assisted Reporting of Electrocardiograms) system previously described in detail (4). Although this system has a diagnostic facility, for the purposes of the present study, left ventricular hypertrophy (voltage only) was defined as being present when the sum of the amplitudes of the S wave in lead V_1 and the R wave in lead V_5 or V_6 was ≥3.5 mV (5), in keeping with the approach used by the Glasgow Blood Pressure Clinic. Left ventricular hypertrophy and strain was defined as ST segment depression ≥0.05 mV and T wave inversion ≥0.1 mV in lead V_5 or V_6 in the presence of the preceding voltage criteria for left ventricular hypertrophy.

Exercise electrocardiography. Exercise was performed on a bicycle ergometer, with a work load commencing at 50 W and increasing by 50 W at 3 min intervals. Exercise was continued until exhaustion. At the end of each stage, blood pressure was measured, a simultaneous 12 lead ECG was recorded with a Siemens-Elema Mingocard 3, and heart rate was estimated from the RR interval. The rate-pressure product was calculated from the product of systolic pressure at peak exercise and maximal heart rate (6). ST depression was defined as horizontal or downsloping depression of the ST segment >0.1 mV 80 ms after the J point (7).

Ambulatory electrocardiographic monitoring. The 24 h ECG was recorded with an Oxford Medilog II FM recorder and analyzed with reference to ventricular arrhythmias. Complex ventricular ectopic beats were defined as follows (8). Early ectopic beats: beats in which the R wave of the ectopic beat commenced before the end of the preceding T wave. Couplets: two consecutive ventricular ectopic beats. Nonsustained ventricular tachycardia: three or more consecutive ventricular ectopic beats occurring at a rate >120 beats/min.

Echocardiography. The echocardiograms were recorded on a Diasonics Cardiovue 3400R phased array scanner with a 2.25 MHz transducer with the patient semisupine in the 45° left lateral position. Measurements of posterior wall and septal thickness and of systolic and diastolic internal ventricular dimensions were made according to the recommendations of the American Society of Echocardiography (9); left ventricular mass was derived from the Penn convention (10). Left ventricular mass index was calculated by dividing the mass by body surface area.

Stress thallium scintigraphy. Exercise was performed on a second occasion according to the same protocol used for the exercise ECG. Eighty megabecquerels (MBq) of thallium-201 were injected at peak exercise through an indwelling antecubital venous cannula. Exercise was continued for 30 to 60 s after injection of the tracer. Imaging began 5 min after injection of thallium-201 with use of a General Electric Maxicamera fitted with a low energy-converging collimeter interfaced to a dedicated minicomputer. Data were acquired in the anterior and 45° and 75° left anterior oblique projections. In each projection, data were acquired in list mode for 600 s with simultaneous recording of the ECG R wave. The images taken were then formatted into an eight frame/cycle gated study. Redistribution images were obtained 4 h later in the same fashion. The studies were analyzed by visual inspection of the gated study. A reversible perfusion defect was defined as an area that showed partial or complete resolution on the redistribution images compared with the poststress images (11). Images that did not change significantly were classified as fixed defects.

Table 1. Comparison of Clinical, Echocardiographic, Excercise and Ambulatory Electrocardiographic Data in Groups I and II

	Group I	Group II
No. of patients	23	23
Mean age (yr)	50	46.3
Systolic BP (mm Hg)	161 ± 24	162 ± 23
Diastolic BP (mm Hg)	94 ± 19	98 ± 14
LV mass index (g/m^2)	180.5 ± 70.5	127.1 ± 27.9*
Exercise data		
Peak systolic BP (mm Hg)	195 ± 33	212 ± 25
Rate-pressure product (× 10^2)	261 ± 81	304 ± 65
Maximal exercise capacity (kpm/min)	659 ± 164	672 ± 172
ST depression	14	4*
Thallium perfusion defect	11	3*
Ambulatory ECG monitoring		
Early ectopic beats	3	3
Couplets	3	3
Nonsustained ventricular tachycardia	2	0

*$p < 0.05$. BP = blood pressure; ECG = electrocardiographic; LV = left ventricular.

Coronary arteriography. Twenty of the 23 patients with ECG left ventricular hypertrophy and strain underwent selective coronary arteriography by the Judkins technique through the right femoral approach (12). The three remaining patients either declined the investigation or were not studied because it was considered unjustified to undertake arteriography because of the presence of other medical problems. A significant coronary stenosis was defined as one in which there was >50% narrowing of luminal diameter.

Statistical analysis. The results were analyzed with a software statistical package designed for use with a DEC PDP 11 computer. Student's *t*, Z and chi-square tests were employed where appropriate. A 5% significance level was used to assess differences between groups with these tests.

All patients gave informed consent to the study, which was approved by the Ethical Committee of Glasgow Royal Infirmary.

Results

Patient subgroups (Table 1). The patients were grouped according to the ECG findings: Group I (n = 23): left

Table 2. Results of Coronary Arteriography in 20 Patients With Electrocardiographic Left Ventricular Hypertrophy and Strain

Group Ia: normal coronary arteries	12
Group Ib: coronary artery disease*	
Single vessel	1
Double vessel	2
Triple vessel	5

*A diseased vessel was defined as one showing a narrowing of >50% of the luminal diameter.

ventricular hypertrophy (voltage criteria) with secondary repolarization abnormalities (ECG left ventricular hypertrophy and strain); Group II (n = 23): normal repolarization (10 with a normal ECG and 13 with voltage only criteria for left ventricular hypertrophy).

The two groups (Group I versus Group II) were similar in age (50 versus 46.3 years), cigarette smoking status (six versus eight smokers), serum cholesterol (5.80 versus 5.83 mmol/liter) and basal blood pressure (161/94 versus 162/98 mm Hg) at the time of the study. Left ventricular mass index was higher in Group I (180.5 ± 70.5 versus 127.1 ± 27.9 g/m^2, $p < 0.05$); it was above the 97th percentile (10) in 20 patients in Group I and in 9 patients in Group II. In all 29 of these patients, the high index was a result of concentric hypertrophy. There were no regional wall motion abnormalities present on two-dimensional echocardiography.

Exercise electrocardiography (Table 1). All patients achieved maximal exercise without chest pain and attained similar peak systolic pressure (195 versus 212 mm Hg), rate-pressure product (261 versus 304 × 10^2) and maximal exercise capacity (659 versus 672 kpm). ST depression at peak exercise was present in 4 patients in Group II and in all 23 patients in Group I. Additional ST depression relative to ST depression at rest was present in 14 patients in Group I and in 4 patients in Group II ($p < 0.05$).

24 hour ambulatory electrocardiographic monitoring (Table 1). The 24 h ambulatory ECG detected high grade ventricular ectopic activity (early ectopic beats and couplets) in three patients in both groups. There were episodes of nonsustained ventricular tachycardia in two patients in Group I (both of whom had coronary artery disease) and none in Group II.

Thallium scintigraphy (Table 1). Fourteen patients had areas of reversible perfusion defects noted in all three views (11 patients in Group I and 3 patients in Group II, $p < 0.05$). A fixed apical defect was present in four patients in Group I and in five patients in Group II.

Coronary arteriography (Table 2). Of the 20 patients in Group I who underwent coronary arteriography, 8 had coronary artery disease (1 with single, 2 with double and 5 with triple vessel disease) and 12 had completely normal coronary arteriograms.

Table 3. Comparison of Clinical, Echocardiographic, Electrocardiographic and Exercise Data in Groups Ia and Ib

	Group Ia	Group Ib
No. of patients	12	8
Mean age (yr)	45	53
Systolic BP (mm Hg)	161 ± 26	159 ± 20
Diastolic BP (mm Hg)	95 ± 15	97 ± 19
LV mass index (g/m^2)	164 ± 49	194 ± 71
Rest ECG configuration		
J point depression	8	6
ST depression	9	6
T wave inversion		
Symmetric	6	4
Asymmetric	6	4
"Overshoot"	6	4
Exercise data		
Peak systolic BP (mm Hg)	198 ± 36	188 ± 31
Rate-pressure product (× 10^2)	267 ± 88	253 ± 80
Maximal exercise capacity (kpm/min)	712 ± 108	581 ± 173*
ST depression	9	5
Thallium perfusion defect	3	8

*$p < 0.05$. Group Ia had normal coronary arteries. Group Ib had angiographic evidence of coronary artery disease. Abbreviations as in Table 1.

Noninvasive detection of coronary artery disease in patients with left ventricular hypertrophy and strain (Table 3). The results of coronary arteriography classified the patients into two subgroups. Group Ia (n = 12) included those with normal coronary arteries; Group Ib (n = 8) included those with asymptomatic coronary artery disease. Comparison of the noninvasive investigations (Group Ib versus Group Ia) demonstrated that patients in Group Ib were slightly older (53 versus 45 years, p = NS), had similar serum cholesterol levels (6.13 versus 5.69 mmol/liter, p = NS) and had a nonsignificantly greater left ventricular mass index (194 versus 164 g/m^2). There were three cigarette smokers in Group Ib and two in Group Ia. Blood pressure at rest (159/97 versus 161/95 mm Hg) and the response to exercise (peak systolic pressure: 188 versus 198 mm Hg; rate-pressure product: 253 versus 267 × 10^2) were similar in the two groups. Despite this, the Group Ib patients (with coronary artery disease) had lower maximal exercise capacity (581 versus 712 kpm, $p < 0.05$). The configuration of the rest ECG (Table 3), with particular reference to the ST-T segments, was similar in the two subgroups. Additional ST segment depression after exercise was common in both subgroups, being present in five patients (62.5%) in Group Ib and in nine patients (75%) in Group Ia.

There were differences in the results of the thallium scintigraphy in the two subgroups. In Group Ia, 9 of the 12 patients with normal coronary arteries had a normal thallium scan and only 3 had a reversible perfusion defect, whereas all 8 patients in Group Ib with coronary artery disease had a

JACC Vol. 13, No. 6
May 1989:1377–81

reversible perfusion defect (Table 3); that is, all patients with normal thallium perfusion had normal coronary arteriograms, and all patients with coronary artery disease had reversible perfusion abnormalities.

Follow-up. Within 1 year of the study's completion five of the eight patients with angiographic coronary artery disease became symptomatic and required intervention in the form of coronary artery bypass grafting (four patients) or percutaneous transluminal coronary angioplasty (one patient).

Discussion

It is now well established that electrocardiographic (ECG) left ventricular hypertrophy and strain is an ominous prognostic factor in patients with hypertension. This increased risk cannot be explained solely on the basis of greater degrees of blood pressure elevation (1,2) and, therefore, other explanations such as myocardial ischemia and ventricular arrhythmia require to be explored.

Myocardial ischemia in hypertension and left ventricular hypertrophy. Myocardial ischemia as a consequence of an increase in left ventricular mass could explain both the ST-T wave changes and the increased mortality from clinical ischemic events. However, associated coronary artery disease could also contribute significantly to the increased risk in these patients. Identification of such patients is clearly important because the association of an increased left ventricular mass with coronary artery disease would identify a high risk subgroup. Eight of the 20 patients with left ventricular hypertrophy and strain on the ECG had significant coronary artery disease despite having no clinical symptoms of ischemic heart disease or a previous history of myocardial infarction.

It would have been of value to have known the coronary anatomy of an age-matched asymptomatic group from the general population and of our Group II patients (with no ST-T wave abnormalities), but this was not feasible for ethical reasons. There is, however, supportive evidence to indicate that the 40% prevalence of coronary artery disease in the Group I patients (with ST-T wave abnormalities) was considerably higher than in the asymptomatic general population. First, postmortem studies (13) of 23,996 asymptomatic patients have shown a prevalence of coronary artery disease of only 4.0%. Second, in the same institution as the present study, only 2 of 76 patients who had routine coronary arteriography for the assessment of aortic and mitral valve disease had asymptomatic coronary artery disease (14). Third, of the last 23 patients with left ventricular hypertrophy due to aortic valve disease who underwent aortic valve replacement in our institution, none had asymptomatic coronary artery disease (A. Riyami, unpublished data). We are, therefore, confident that the prevalence of coronary artery disease was higher in Group I patients than in the general population.

We also believe that the prevalence of coronary artery disease was lower in Group II patients, of whom only three had a reversible thallium perfusion defect. Thallium scintigraphy had excellent negative predictive value in all patients with normal coronary arteries and a normal thallium scans. Because 20 of the 23 patients in Group II had normal findings on thallium scintigraphy, it is likely that the prevalence of coronary artery disease was lower in this group. Even if the three patients with a positive thallium scan had coronary artery disease, the prevalence rate would have been only 13%.

Three patients in Group I had a reversible thallium perfusion defect in the presence of normal coronary arteries. This may be a result of areas of subendocardial ischemia through similar mechanisms as those described in patients with left ventricular hypertrophy due to aortic stenosis (15,16). Possible explanations for this relative myocardial ischemia in left ventricular hypertrophy are, first, that the myocardium grows proportionally more than the capillary bed with a resultant decreased capillary density (17). Second, there is an alteration in coronary artery hemodynamics with increased coronary artery resistance and decreased coronary vascular reserve in patients with hypertensive left ventricular hypertrophy (18).

A number of additional findings emerged from the noninvasive investigations. It has been suggested that symmetry of the T wave inversion in patients with left ventricular hypertrophy and strain is associated with myocardial ischemia, whereas asymmetric T waves, J point depression and "overshoot" of the T wave above the isoelectric line are manifestations of increased mass without ischemia (19). This was not the finding of our study. In our patients, the ST-T wave configuration in the patients with coronary artery disease was the same as that in patients with normal coronary arteries. Furthermore, in the patients with left ventricular hypertrophy and strain, accentuation of the ST-T wave abnormalities on exercise did not correlate with the presence of coronary artery disease, nor did blood pressure, peak heart rate or rate-pressure product, although, as would be expected, these tended to be lower in the patients with coronary artery disease. Chest pain during exercise testing was not a feature in either of the patient groups studied, and it was clear that the exercise tolerance test in the absence of the thallium scan was of no help in predicting the presence of coronary artery disease.

Ventricular arrhythmias. Our results with ambulatory ECG monitoring differ from those of previous reports of an increased incidence of ventricular arrhythmias in patients with left ventricular hypertrophy. The incidence of high grade ventricular ectopic activity was similar in patients with and without left ventricular hypertrophy and strain; three patients in both groups had complex ventricular ectopic

beats. This finding was in contrast to the observations of Messerli et al. (20), who showed a greater frequency of ventricular ectopic activity in patients with echocardiographic left ventricular hypertrophy. In our study, only 2 patients had episodes of nonsustained ventricular tachycardia, whereas in the study of McLenachan et al. (21), 14 of 50 patients with left ventricular hypertrophy had nonsustained ventricular tachycardia.

There are several possible reasons for these differing results. Drug therapy was withdrawn in our study in all patients before the period of ambulatory monitoring, and this procedure may have reduced the number of ectopic beats occurring as a consequence of potassium or magnesium deficiency. Our monitoring period was 24 h compared with 48 h in the study of McLenachan et al. (21). Longer periods of monitoring may increase the detection rate of ventricular arrhythmias (22). In addition and of more importance, patients with symptomatic coronary artery disease were excluded from our study. This is a group in which more arrhythmias might be expected to occur. It was, however, clearly an advantage in our study to know the coronary anatomy in all patients with left ventricular hypertrophy and strain. Nonsustained ventricular tachycardia was not observed in any of the patients with normal coronary arteries.

Noninvasive detection of asymptomatic coronary artery disease. Because sudden death is often the first manifestation of coronary heart disease in patients with hypertension and left ventricular hypertrophy and strain (1), those patients most at risk would have to be identified at a preclinical stage of the disease for their outlook to be improved by interventions such as coronary artery surgery or angioplasty. It is not feasible to perform coronary arteriography in all patients with ECG left ventricular hypertrophy and strain. There is a need, therefore, for a noninvasive technique to identify those patients most at risk. In our study, stress thallium scintigraphy was found to be a valuable technique for detecting unsuspected coronary artery disease in this group of patients; sensitivity was 100%, specificity was 75% and overall predictive accuracy was 85%.

Conclusions. Hypertensive patients with ECG left ventricular hypertrophy and strain have a high incidence of asymptomatic but significant coronary artery disease. This cannot be identified by standard exercise testing, Holter ECG monitoring or the configuration of rest ST-T changes. However, the presence of reversible perfusion abnormalities during thallium scintigraphy is of diagnostic value, and this study should be considered in all patients with left ventricular hypertrophy and strain as a means of detecting a potentially high risk subset in this group of hypertensive patients.

We thank Evelyn Tibbs for her technical assistance during this study.

References

1. Kannel WB, Gordon T, Castelli WP, Margolis JR. Electrocardiographic left ventricular hypertrophy and risk of coronary heart disease: the Framingham Study. Ann Intern Med 1970;72:813–22.
2. Kannel WB, Abbott RD. A prognostic comparison of asymptomatic left ventricular hypertrophy and unrecognized myocardial infarction: the Framingham Study. Am Heart J 1986;111:391–7.
3. Macfarlane PW. The British Regional Heart Study: the electrocardiogram and risk of myocardial infarction on follow-up. J Electrocardiol 1987; 20(suppl):53–6.
4. Macfarlane PW, MacFarlane DK, Podolski M, Lawrie TDV. The ECG analysis programme for the Mingocare system. Electromedica 1984;52: 126–36.
5. Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy as obtained by the unipolar precordial and limb leads. Am Heart J 1949;37:161–86.
6. Fortuin NJ, Weiss JL. Exercise stress testing. Circulation 1977;56:699–712.
7. Martin CM, McConahay DR. Maximal treadmill exercise electrocardiography: correlations with coronary arteriography and cardiac hemodynamics. Circulation 1972;46:956–62.
8. Lown B, Wolf M. Approaches to sudden death from coronary heart disease. Circulation 1971;44:130–42.
9. Sahn DJ, Demaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 1978;58:1072–83.
10. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man: anatomic validation of the method. Circulation 1977;55:613–8.
11. Tweddel AC, Martin W, McGhie AI, Simpson I, McKillop JH, Hutton I. Ventricular function and perfusion by gated thallium scanning. In: Hofer R, Bergmann H, eds. Radioaktive Isotope in Klinik und Forschung. Vienna: H. Egermann, 1984;16:409–14.
12. Judkins MP. Selective coronary arteriography: a percutaneous transfemoral technique. Radiology 1967;89:815–24.
13. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary artery disease. N Engl J Med 1979;300:1350–8.
14. Baxter RH, Reid JM, McGuiness JB, Stevenson JG. Relation of angina to coronary artery disease in mitral and in aortic valve disease. Br Heart J 1978;40:918–22.
15. Bailey IK, Come PC, Kelly DT, et al. Thallium-201 myocardial perfusion imaging in aortic valve stenosis. Am J Cardiol 1977;40:889–99.
16. McKillop JH, Murray RG, Turner JG. Thallium-201 imaging in aortic valve disease. Schmidt HAE, Berrocal JO, eds. Proceedings of the Society of Nuclear Medicine, 16th International Annual Meeting, Stuttgart, New York: F. K. Shattauer Verlag, 1979:458–60.
17. Breisch EA, Houser SR, Carey RA, Spann JF, Bove AA. Myocardial blood flow and capillary density in chronic pressure overload of the feline left ventricle. Cardiovasc Res 1980;14:469–75.
18. Strauer B. Ventricular function and coronary hemodynamics in hypertensive heart disease. Am J Cardiol 1979;44:999–1006.
19. Beach C, Kenmure ACF, Short D. Electrocardiogram of pure left ventricular hypertrophy and its differentiation from lateral ischaemia. Br Heart J 1981;46:285–9.
20. Messerli FH, Ventura HO, Elizardi DJ, Dunn FG, Frohlich ED. Hypertension and sudden death: increased ventricular ectopic activity in left ventricular hypertrophy. Am J Med 1984;77:18–22.
21. McLenachan JM, Henderson E, Morris KI, Dargie HJ. Ventricular arrhythmias in patients with hypertensive left ventricular hypertrophy. N Engl J Med 1987;317:787–92.
22. Winkle RA, Peters F, Hall R. Characterization of ventricular tachyarrhythmias on ambulatory ECG recordings in post-myocardial infarction patients: arrhythmia detection and duration of recordings, relationship between arrhythmia frequency and complexity and day-to-day reproducibility. Am Heart J 1981;102:162–9.